UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,952	03/22/2002	Stephen H. Leppla	15280-4051US	4741

7590 10/05/2007

Annette S Parent
Townsend & Townsend & Crew
8th Floor
Two Embarcadero Center
San Francisco, CA 94111-3834

EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,952	LEPPLA ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9,11-14,18-22 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,9,11-14,18-22 and 25-30* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/20/2007 has been entered.

Claims 1, 7, 9, 11-14, 18-22 and 25-30 are currently pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 11-14, 18-22 and 25-30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (IDS, 1997, *of record*) as evidenced by Klimpel et al. (PNAS 1992; 89: 10277-10281, *of record*) in view of Bayley *et al.* (IDS, 1998, *of record*), Dano (US 5,519,120, 1996), and Coombs et al. (J. Biol. Chem. 1998; 273: 4323-4328).

Leppla *et al.* teach (column 115, lines 41-63) a method for targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: a) administering to the cell population a first compound comprising a first protein consisting essentially of: i) the translocation domain and the anthrax lethal factor (LF) binding domain of the native anthrax protective antigen (PA) protein, and ii) a ligand domain that specifically binds the first protein to a target on the surface of the cell population to bind the first compound to said surface; and b) administering to the resultant cell population a second compound comprising a fusion protein or conjugate consisting essentially of: i) the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein, chemically attached to ii) a biological activity-inducing polypeptide to bind the second compound to the first compound on the

surface of the cell population, internalize the second compound into the cell population, and effect the activity of the polypeptide therein. The patent further teaches (Column 116, lines 42-44, 53-56, and 63-64) that the ligand domain of the first compound can be either the ligand domain of the native anthrax protective antigen (PA) protein or growth factor, or an antibody, wherein the antibody is a single chain antibody. Furthermore, Leppla *et al.* disclose (column 115, lines 64-67 and column 116, lines 40-41) that the anthrax protective antigen (PA) binding domain of the second compound comprising at least the first 254 amino acid residues but less than all of the amino acid residues of the native anthrax lethal factor. Moreover, the patent teaches (column 116, lines 51-52) that the second compound may comprise the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein chemically attached to a polypeptide through a peptide bond. In addition, Leppla *et al.* teach (column 116, lines 49-52 and 57-62) that the polypeptide of the second compound is an enzyme or a toxin, wherein the toxin can be Pseudomonas exotoxin A (PE), A chain of Diptheria toxin, or shiga toxin. With regards to Pseudomonas exotoxin A, the patent teaches (column 17, lines 15+) that anthrax lethal toxin is linked to the ADP-Ribosylation Domain of Pseudomonas exotoxin. Leppla *et al.* also disclose (Abstract, last sentence) proteins including an anthrax protective antigen which has been mutated to replace the trypsin cleavage site with residues recognized specifically by the HIV-1 protease. Specifically, the patent teaches (column, 11, lines 10-13) PA proteins which have been mutated to replace R164 to 167 with an amino acid sequence recognized by the HIV-1 protease. In addition, the patent teaches (column 1, lines 24-26) that in a therapeutic or diagnostic setting, the used of an sFv may offer attractive advantages over the use of monoclonal antibodies. Lastly, Leppla *et al.* teach (column 15, lines 27-37) that this methodology can be used to specifically kill a tumor cell in a subject. Thus while Leppla et al. do not specifically teach that amino acid residues R164-167 is the furin recognized cleavage site of native protective antigen, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art because as evidenced by Klimpel et al. residues 164 to 167 of PA is a furin recognized cleavage site (abstract).

Leppla *et al.* does not disclose a mutated protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site. Nor do Leppla et al. teach that the cancer is a carcinoma or fibrosarcoma.

Bayley *et al.* teach (column 12, lines 13+) the construction of Ab-αHL conjugates and mutated two chain αHL conjugates, wherein a protease can be employed as an activator of inactive compounds, e.g. plasminogen activator, specifically urokinase-type plasminogen activator (uPA). Specifically, the patent teaches (column 12, lines 13+) that because cancer cells have been shown to secrete plasminogen activator, the protease cleavage site for plasminogen activator can be incorporated into the conjugate for specific activation of this cell type. In addition, the patent teaches that uPA is highly expressed in melanoma cells (column 13, lines 1-5).

Dano et al. teach that u-PA has been found in extracts from human lung, colon, endometrial, breast, prostate and renal carcinomas, human melanomas, murine mammary tumors, and the murine lewis lung tumors, as well as in invasively growing and metastasizing Lewis lung carcinomas and fibrosarcoma cells (Column 1, lines 57-65 and column 9, lines 11-13).

Coombs et al. teach the importance of target site mobility and primary sequence for selective cleavage of engineered protein substrates by t-PA and uPA, wherein residues 44-55 of staphylococcal nuclease (Snase) were replaced with optimal t-PA or u-PA cleavage sites (page 4324, 1st column, 1st full paragraph). In particular, the references teaches that both t-PA and u-PA efficiently cleaved the engineered Snase variants despite substrate loop constraint and exhibit the same relative sequence selectivity observed for cleavage of peptide substrates, confirming that proteins can be engineered to be selectively liable to t-PA or u-PA.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to incorporate a plasminogen activator-protease cleavage site in place of the native protective antigen furin-recognized cleavage site as taught by Leppla et al. for the purposes of targeting a compound to a carcinoma or fibrosarcoma in view of the teachings of Bayley et al., Dano et al., and Coombs et al. One would have been motivated to do so because in view of Bayley *et al.* teach that it is well known in the art that a plasminogen activator, such as uPA, can be employed as an activator of an inactive agent; and further, Coombs et al. teach that proteins can be engineered to be selectively liable to u-PA. Moreover, as taught by Dano et al., it is well known with to those of skill in the art that u-PA is expressed in human lung, colon, endometrial, breast, prostate and renal carcinomas, human melanomas, murine mammary tumors, and the murine lewis lung tumors, as well as in invasively growing and metastasizing Lewis lung carcinomas and fibrosarcoma cells. One of ordinary skill in

the art would have reasonable expectation of success that by incorporating a plasminogen activator-protease cleavage site in place of the native protective antigen furin-recognized cleavage site as taught by Leppla et al. for the purposes of targeting a compound to a carcinoma or fibrosarcoma in view of the teachings of Bayley et al., Dano et al., and Coombs et al., one would achieve a method of specifically targeting a compound to a carcinoma or fibrisarcoma cancer cell.

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments pertaining to the previous rejection as they relate to the instant rejection. In response to the previous rejection, Applicants assert that the combined references do not teach each and every element of the claimed invention. For example, Applicants assert that while Leppla discloses killing tumor cells in a subject and Bayley teaches a single type of cancer cell-melanoma, neither reference teaches or suggest the claimed invention as currently amended which is drawn to targeting carcinoma or fibrosarcoma cells. Moreover, Applicants assert that the skilled artisan would have no reasonable expectation of success in combining the cited references. Specifically , Applicants assert that Bayley discloses hypothetically that antibody-aHL conjugates containing a tumor specific protease cleavage sequence might be used to generate an active pore forming agent upon cleavage by a tumor specific protease and suggest that uPA might be a tumor specific protease, citing its expression in metastatic tumor cells, with the reference to a single cancer cell type-melanoma. On the other hand, Applicants assert that Leppla teaches killing a tumor cell by administration of a first fusion protein comprising the translocation domain and LF binding domain of the native PA protein and a tumor cell specific ligand domain, but is silent on switching the native furin site with a tumor specific protease site. Moreover, Applicants assert that the principal disclosure of Leppla is directed to the treatment of HIV infected cells, using a PA protein in which the furin cleavage site has been replaced with the HIV-1 protease site. Thus, Applicants assert that the disclosure of the cited references would not provide the skilled artisan with a reasonable expectation of success in combining the cited references to arrive at the presently claimed invention. In particular, Applicants assert that the skilled artisan would recognize that in order to solve the problem of targeting a compound to a cancer cell over expressing uPA and uPAR, the cells must express uPA and uPAR, the secreted uPA must be in sufficient proximity and in the right three dimensional configuration to the mutant protective antigen containing a uPA-recognized cleavage site in order to effect cleavage, and the non-natively disposed uPA-recognized cleavage site on the mutant antigen

must be in the proper three dimensional configuration to allow recognition and cleavage by the uPA/uPAR complex, as explained by Dr. Leppla (see Declaration). As such, Applicants assert that given the highly structured nature of uPA's normal plasminogen substrate, the skilled artisan would doubt that the proper structure of the uPA cleavage site would be maintained upon engrafting it onto an unrelated protein. Next, Applicants assert that the Examiner appears to be using impermissible hindsight reconstruction in combining these references because as discussed in Dr. Leppla's declaration, the references would fail to suggest to the skilled artisan the desirability of placing the uPA cleavage site in the context of protective antigen. Lastly, Applicants assert that Dr. Leppla's declaration provides objective secondary evidence of non-obviousness which as discussed by the Court in KSR, such evidence of unexpected or surprising results provides a strong indication of non-obviousness. Thus, Applicants submit that Dr. Leppla's previously submitted declaration unequivocally demonstrates that the claimed mutant protective antigens are surprisingly effect for the delivery of a compound to tumors overexpressing uPA in vivo (see Declaration, § 8), for instance, to cancer cells, carcinoma and fibrosarcoma, as currently recited in the amended claims.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions that the Leppla et al. and Bayley et al. do not teach each and every element of the claimed invention, the Examiner acknowledges and concedes that Leppla et al. and Bayley et al. do not specifically teach carcinoma or fibrosarcoma. However, the Examiner recognizes that the teachings of Dano et al., as described above, remedy these deficiencies. Regarding Applicants assertions that the skilled artisan would have not reasonable expectation of success in combining the cited references because Bayley et al. discloses a hypothetical antibody – aHL conjugate containing a tumor specific protease cleavage sequence and Leppla et al. principal disclosure is directed towards treatment of HIV infected cells, the Examiner recognizes that patents are relevant as prior art for all they contain and may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277

(CCPA 1968)). Moreover, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the ad, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, Leppla et al. disclose targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising administering a protective antigen which has been mutated to replace the "native" trypsin cleavage site, e.g., furin cleavage site, with residues recognized specifically by the HIV-1 protease, wherein this methodology can be applied to specifically killing a tumor cell in a subject, whereas Bayley et al. teach that the incorporation of a uPA recognized cleavage site into an inactive compound is made active by a plasminogen activator expressed on the cell surface of tumor cells. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the protective antigen as taught by Leppla et al. to include a uPA cleavage site in place of the furin cleavage site in view of the teachings of Bayley et al., one would achieve a method of specifically targeting tumor cells which express uPA in a subject. Regarding Applicants arguments with respect to what one of skill in the art would recognize, the Examiner acknowledges Applicants contention that one of skill in the art would recognize that in order to solve the problem of targeting a compound to a cancer cell over expressing uPA and uPAR, the cell must express uPA and uPAR, the secreted uPA must be in sufficient proximity and in the right three dimensional configuration to the mutant protective antigen containing a uPA-recognized cleavage site and the non-natively disposed uPA-recognized cleavage site on the mutant antigen must be in the proper three dimensional configuration to allow recognition and cleavage of uPA/UPAR complex. However, as explained in the prior office action, one of the three requirements for a 103 rejection is a **reasonable, not absolute**, expectation of success in view of the references cited. In the instant

case, those of skill in the art recognizes that insertion of protease cleavage sites into a biologically active conjugate enables specific activation of the conjugate by cells which express or secrete this particular protease as taught by Bayley et al. Moreover, as taught by Coombs et al., proteins can be engineered to be selectively liable to t-PA or u-PA. Thus, while the Examiner concedes that the factors outlined by Applicants need to be considered prior to insertion of a protease cleavage site, in view of the teachings of Bayley et al. and Coombs et al., one would have a reasonable, not absolute, expectation of success in view of the references cited. With regards to Applicants assertions that the data presented in Dr. Leppla's declaration is evidence of nonobviousness based on unexpectedly advantageous properties, the Examiner acknowledges Applicants allegations that there were unexpected results. However, the Examiner has carefully reviewed the Leppla Declaration and cannot find any basis for Applicants assertions of "unexpected advantageous properties". For example, the declaration presents experiments which demonstrate that the mutant protective antigens of the presently claimed invention are particularly effective for delivering a compound to target cells in vivo which amounts to a general allegation that the claims define a patentable invention (Declaration, page 4). However, the Declaration does not appear to set forth whether the effective delivery of a compound to tumors overexpressing uPA in vivo is really unexpected and does not appear to point out how the language of the claims patentably distinguishes them from the references. As such, Applicants allegations with respect to unexpected results, e.g., properties, are considered moot. Lastly, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Coombs et al., considered the closest prior art to claim 7, teaches a uPA cleavage site consisting of the amino acid sequence PGSGRSAG (page 4325, Table 1). However, the prior art does not appear to provide any motivation to remove the glycine from the prior arts sequence to

arrive at the claimed invention. As such, Claim 7 appears to be free of the prior art, but is objected to as being dependent from a rejected independent claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF